(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau





(43) International Publication Date 24 December 2003 (24.12.2003)

PCT

(10) International Publication Number WO 03/105855 A1

A61K 31/535, (51) International Patent Classification7: 31/40, C07D 265/30, 207/02, A61P 43/00

(21) International Application Number: PCT/US03/18482

(22) International Filing Date: 12 June 2003 (12.06.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

14 June 2002 (14.06.2002) US 60/388,621 60/403,830 15 August 2002 (15.08.2002) US 15 November 2002 (15.11.2002) US 60/426,940 60/458,318 28 March 2003 (28.03.2003) US

(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ARRINGTON, Kenneth, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). COLEMAN, Paul, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). COX, Christopher, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). FRALEY, Mark, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). GARBACCIO, Robert, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). HARTMAN, George, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). HOFFMAN,

William, F. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). TASBER, Edward, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

with international search report

before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MITOTIC KINESIN INHIBITORS

(57) Abstract: The present invention relates to dihydropyrrole compounds that are useful for treating cellular proliferative diseases, for treating disorders associated with KSP kinesin activity, and for inhibiting KSP kinesin. The invention also related to compositions which comprise these compounds, and methods of using them to treat cancer in mammals.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/18482

A. CLASSIFICATION OF SUBJECT MATTER				
IPC(7) : A61K 31/535, 31/40; C07D 265/30, 207/02; A61P 43/00 US CL : 514/237.5, 423; 544/162; 548/538				
	International Patent Classification (IPC) or to both na	ional classification and IPC		
B. FIEL	DS SEARCHED			
Minimum documentation searched (classification system followed by classification symbols) U.S.: 514/237.5, 423; 544/162; 548/538				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched EAST, WEST				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN-CAS online				
C. DOC	UMENTS CONSIDERED TO BE RELEVANT			
Category *	Citation of document, with indication, where a	propriate, of the relevant passages Relevant to claim No.		
*	US 3,644,414 (HELSEY et al) 22 February 1972 (22	2.02.1972), see entire reference. 11, 12 and 16-42		
	documents are listed in the continuation of Box C.	See patent family annex.		
	pecial categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the		
	defining the general state of the art which is not considered to be lar relevance	principle or theory underlying the invention		
·	plication or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone		
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		"Y" document of particular relevance; the claimed invention causes be considered to involve an inventive step when the document is combined with one or more other such documents, such combination		
"O" document	referring to an oral disclosure, use, exhibition or other means	being obvious to a person skilled in the art		
	published prior to the international filing date but later than the ate claimed	"&" document member of the same patent family		
Date of the actual completion of the international search D		Date of mailing of the international search report		
14 November	r 2003 (14.11.2003)	Authorized officer 9 1 DEC 2003		
Name and mailing address of the ISA/US		Authorized officer VIDE C 2003		
Mail Stop PCT, Attn: ISA/US Commissioner for Patents		Andrea D Small		
P.O. Box 1450		Telephone No. (703) 308-1234		
	xandria, Virginia 22313-1450 b. (703)305-3230	Telephone 110. (100) 300-1234		

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/18482

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)			
This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:			
Claim Nos.: because they relate to subject matter not required to be searched by this Authority, namely:			
Claim Nos.: 1-10, 13-15 and parts of 11 and parts of 16-42 because they relate to parts of the international application that do not comply with the prescribed requirements to san extent that no meaningful international search can be carried out, specifically: Please See Continuation Sheet	uch		
Claim Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.	4(a).		
Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)			
This International Searching Authority found multiple inventions in this international application, as follows:			
 As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 	×rt		
4. No required additional search fees were timely paid by the applicant. Consequently, this international search reportestricted to the invention first mentioned in the claims; it is covered by claims Nos.:	t is		
Remark on Protest The additional search fees were accompanied by the applicant's protest.			
No protest accompanied the payment of additional search fees.			

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

Continuation of Box 1 Reason 2: In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly crediess permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to regarded as being a clear and consider description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARkicle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		PCT/US03/18482
Continuation of Box 1 Reason 2: In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subre matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.	INTERNATIONAL SEARCH DEPORT	1 0 1 0 0 0 0 1 0 1 0 1
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and theri lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.	INTERNATIONAL SEARCH REPORT	
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and theri lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		J
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		:
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.	,	
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		
In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and their voluminous meanings and their seemingly endless permutations and combinations and their lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		
permutations and combinations and theri lengthly list of divergent compounds in claims 11, 13, 14 and 15, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, be a claimed subject matter. As presented, be a claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.		
determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, Article 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.	In these claims, the numerous variables (e.g. R1, R2, R3, R4, R5, R6, etc.) and the	heir voluminous meanings and their seemingly endless
regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.	permutations and combinations and theri lengthly list of divergent compounds in ci	aims 11, 13, 14 and 15, make it virtually impossible to
requirements of PCT, ARticle 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.	determine the full scope and complete meaning of the claimed subject matter. As j	presented, the claimed subject matter cannot be
discernable inventions, namely the first 18 species named in claim 11, claim 12 in its entirety and parts of claims 16-42 that read on these named compounds.	regarded as being a clear and concise description for which protection is sought an	d as such the listed claims do not comply with the
named compounds.	requirements of PC1, Akticle o. Thus it is impossible to carry out a meaningful s	its entirety and mosts of alaims 16.42 that read on these
		its entirety and parts of claims 16-42 that read on these
	named compounds.	
		İ
		j
		·

Form PCT/ISA/210 (second sheet) (July 1998)